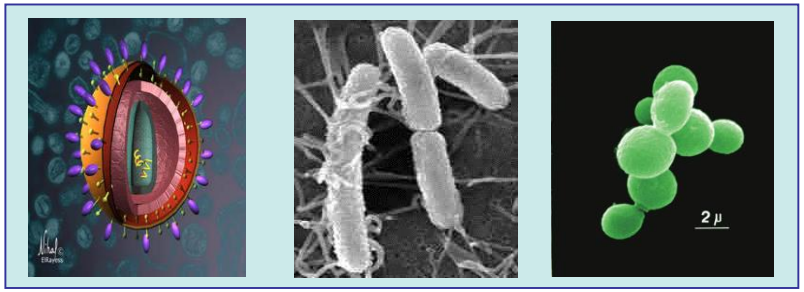
Centre d'Infection & d'Immunité de Lille

Institut Pasteur de Lille
Vivre mieux, plus longtemps

The immunology of influenza and bacterial superinfection



30h November 2017-GEIG 2017

Instituts thématiques
Inserm
Institut national de la santé et de la recherche médicale

Université de Lille

CNRS

Centre d'Infection & d'Immunité de Lille

Lung Infection and Innate Immunity

Institut Pasteur de Lille — Vivre mieux, plus longtemps

Secondary bacterial infection in the context of pulmonary inflammation

→ **Acute inflammation: influenza**

→ **Chronic inflammation: COPD**

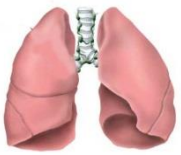
* **Unravel mechanisms leading to enhanced susceptibility**

* **Exploit the knowledge to propose therapies**

Influenza A virus

* **Annual influenza epidemics affects 5 to 15% of world population (H1N1, H3N2)**

* **Correlation between the degree of lung inflammation and morbidity/mortality**

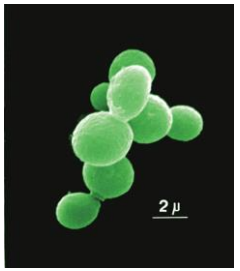


* **Increased susceptibility to secondary bacterial infection can occur during IAV epidemics and pandemics**

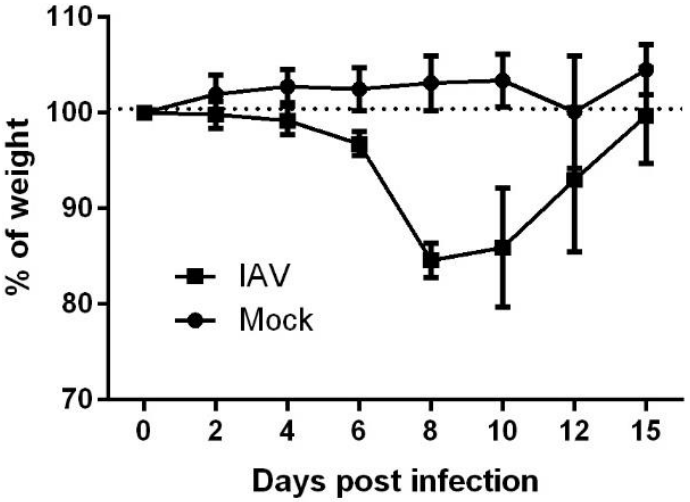
***e.g.*: 1918–1919 (Spanish flu, ~20-40 million deaths worldwide)**

→ ***Streptococcus pneumoniae (pneumococcus)***

The mechanisms include alterations of mechanical (epithelial damage) and immunological (innate response) defences

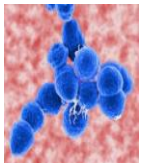


Role of Natural Killer T lymphocytes during influenza and secondary bacterial infection



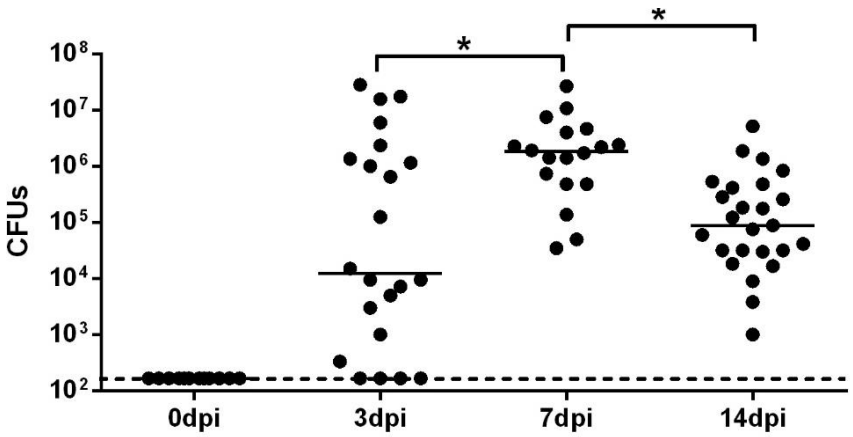
IAV
H1N1 H3N2
(sublethal)

S. pneumoniae
(sublethal)

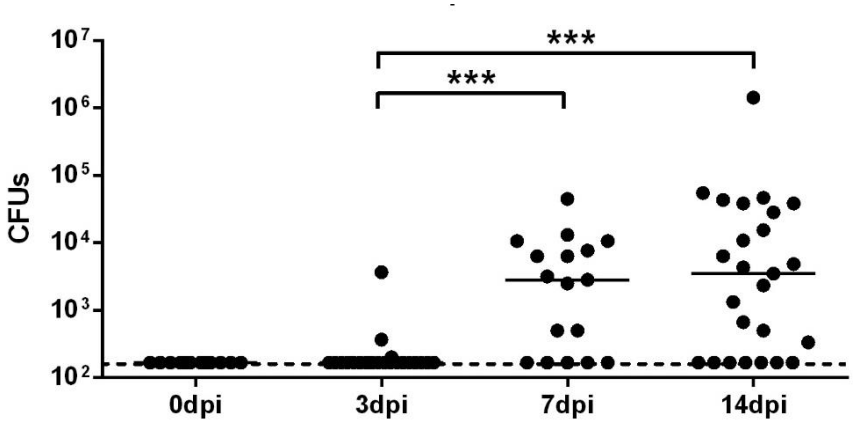


H3N2/Sp1

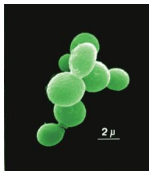
Lung



Spleen



C. Paget

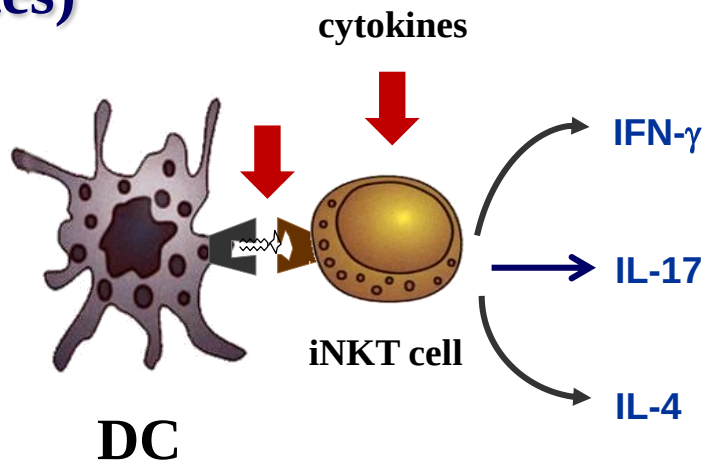


S. Ivanov

Role of Natural Killer T lymphocytes (NKT) during influenza and secondary bacterial infection

- **Very reactive to the environment**
  (sentinel role in mucosal sites)

- **Therapeutic potentials**
  (alpha-galactosylceramide)



Muc Immunol (2013), Plos Pathogen (2014), Cancer Research (2014)

Natural Killer T lymphocytes play an early positive role during influenza and secondary bacterial infection

iNKT cells are beneficial during experimental IAV infection

H1N1/PR8

De Santo et al . JCI (2008)
Kok et al . J. Leukol. Biol (2011)
Maazi et al . Plos One (2013)

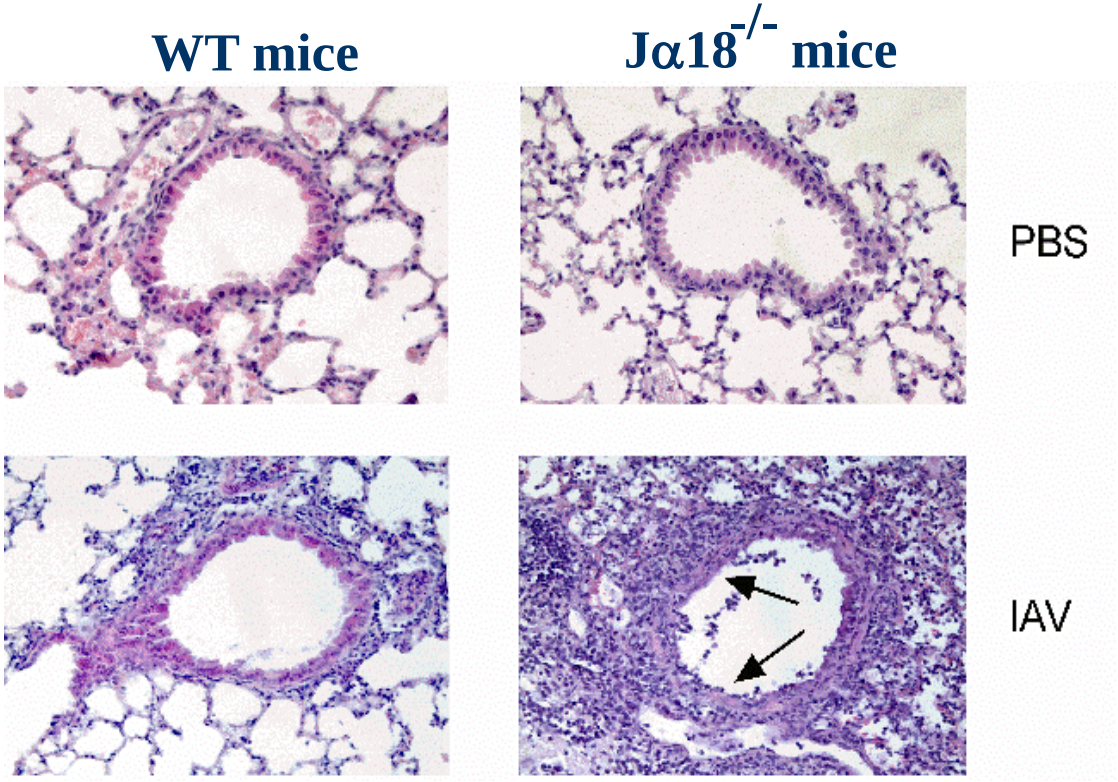
→ **CTL response (through MDSCs, DCs)**

H3N2/Scotland/20/74

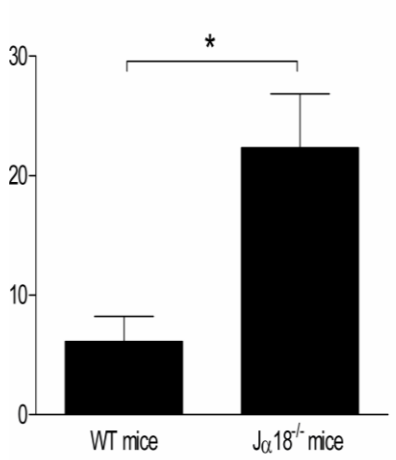
Paget et al . J. Immunol (2011)

→ **Control of pneumonia**

iNKT cells protect the airway epithelium



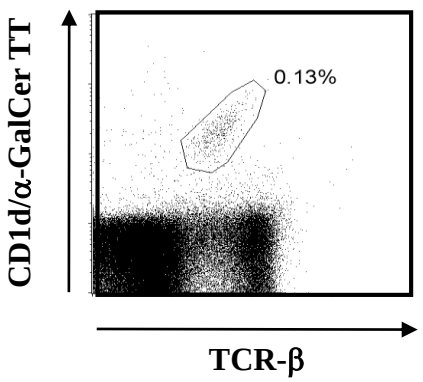
Pathology scores

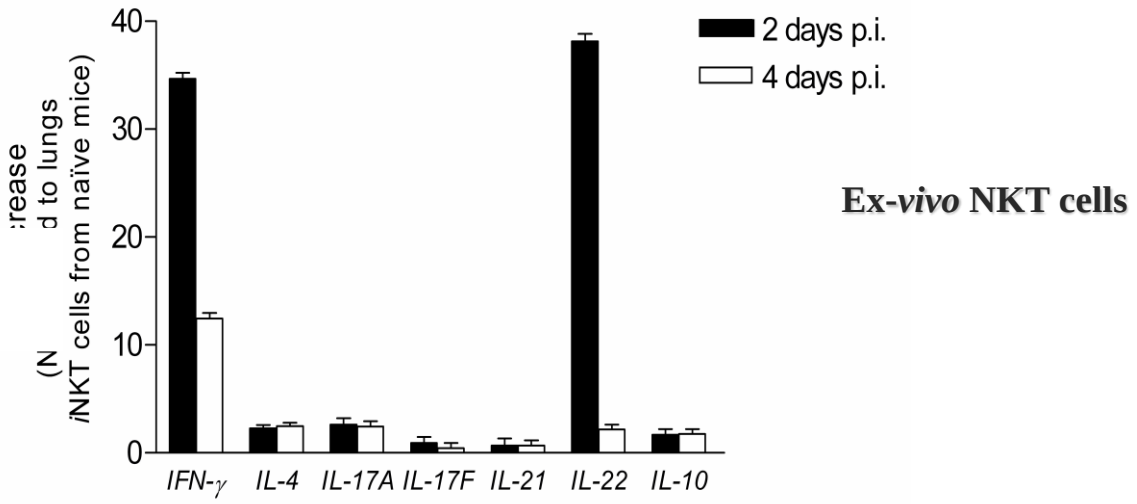


Paget et al . J. Immunol (2011)

Impaired epithelial integrity

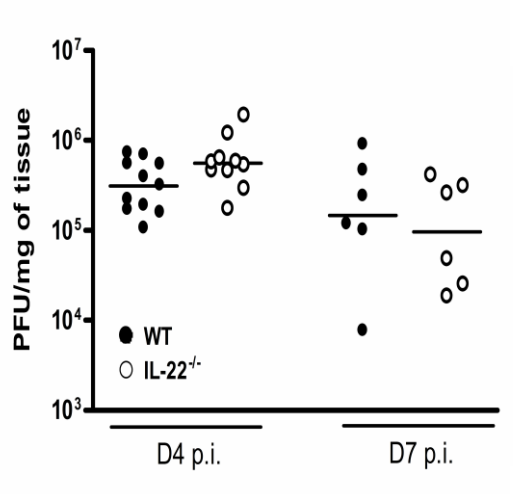
Lung NKT cells is a major source of IL-22 during early IAV infection





Ex-*vivo* NKT cells

WT vs *Il22*$^{-/-}$

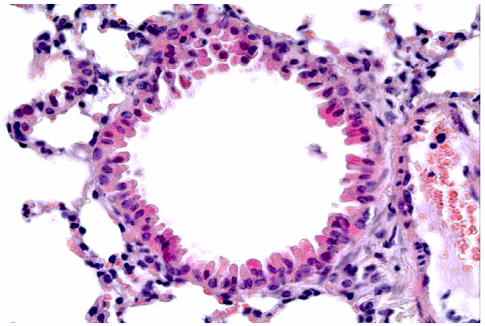


No change in viral load

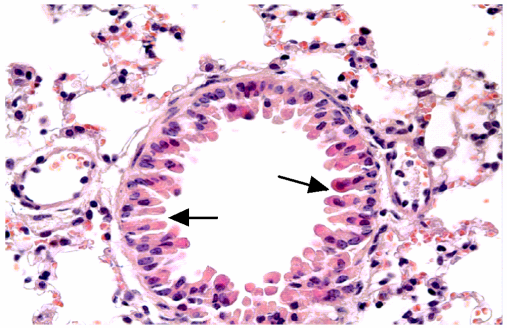
More epithelial damage in *Il22*-/- mice

IAV

WT



IL-22-/-



Paget et al. (2012) J. Biol. Chem

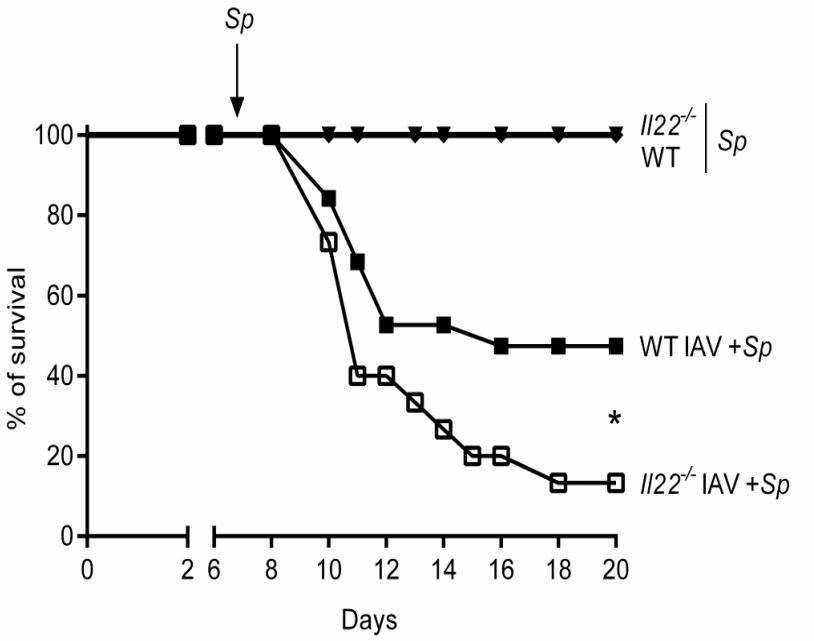
IL-22 limits secondary bacterial infection

Day 7

WT *versus* IL22 KO

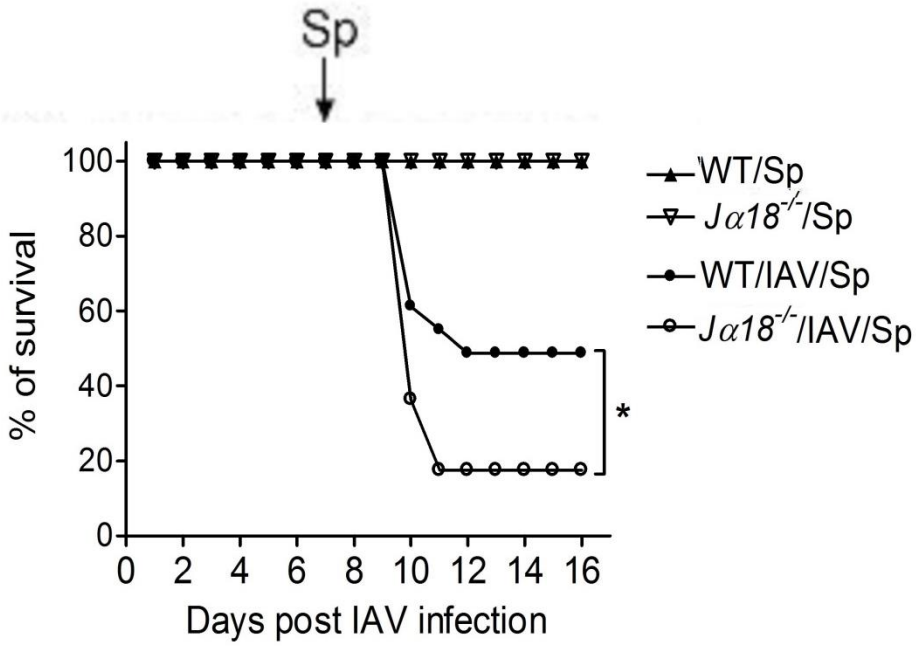
IAV (50 PFUs)
(sublethal)

S. pneumoniae
1 x 10^3 CFUs



Enhanced CFUs in Il-22-/-

Ivanov et al . J. Virol (2013)



Enhanced CFUs in Ja18-/-

Barthelemy et al . Muc. Immunol (2016)

Role of iNKT cells in secondary bacterial infection post-influenza

IAV

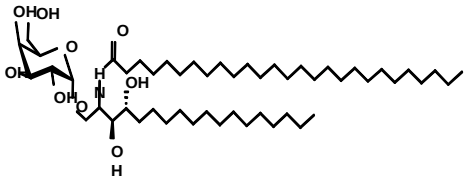
NKTs

IL-22

Epithelial repair

S. pneumoniae

NKTs

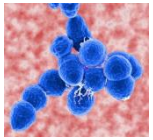


α-GalCer

Therapeutic application?

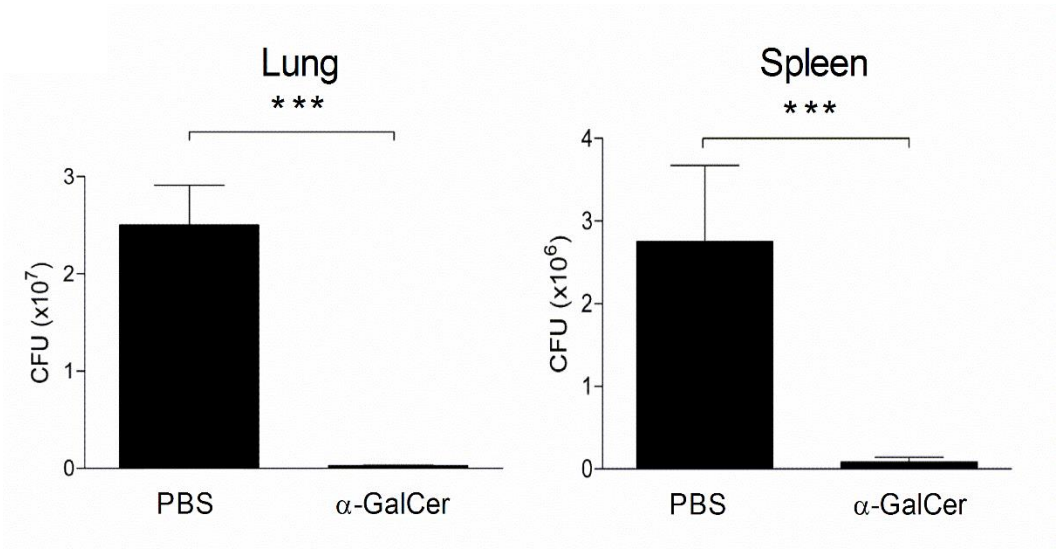
α-GalCer is protective in mice only infected with *S. pneumoniae*

Sp only

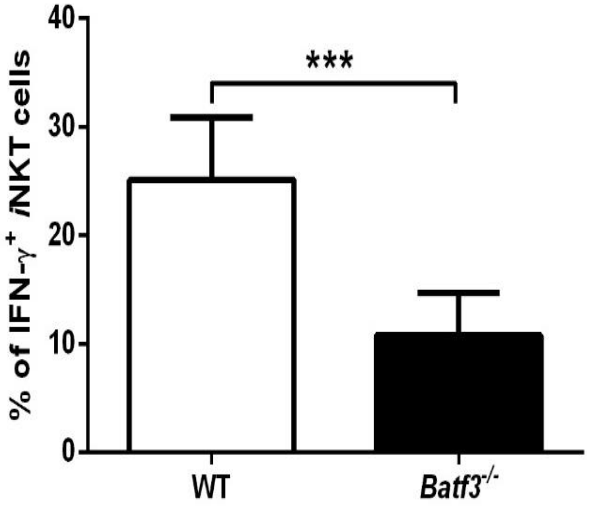


α-GalCer
16hrs before

Sp
10^6 CFU



cDC1 are neccessary for iNKT cell activation (naive mice)

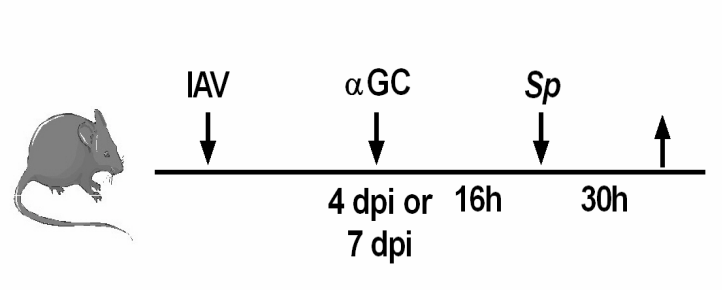


Baft3-/-: no CD103+ cDC

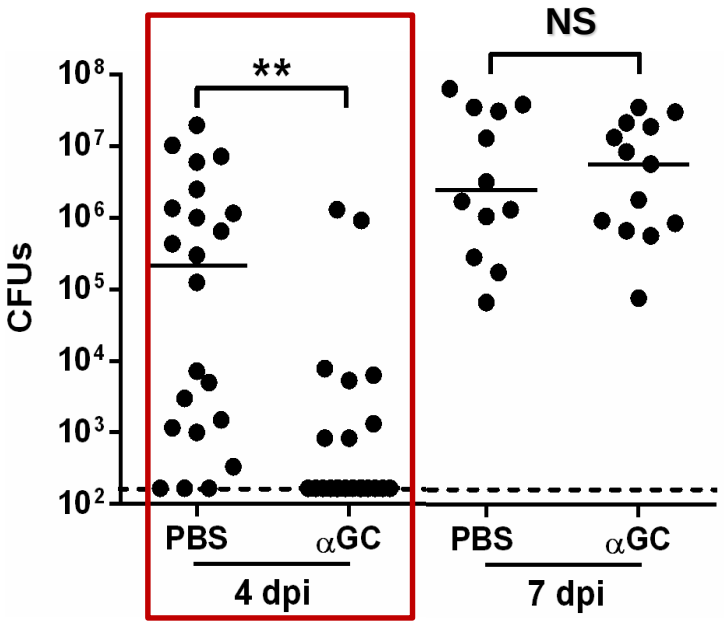
Ivanov et al (2012). JID

α-GalCer protects against superinfection early after IAV infection

Sp/IAV

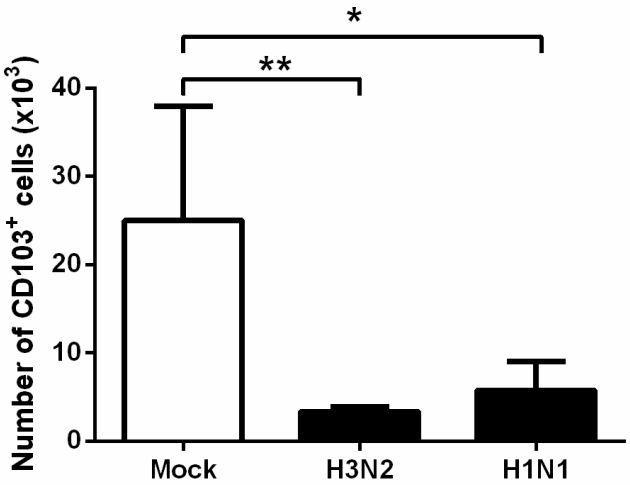


H1N1p or H3N2

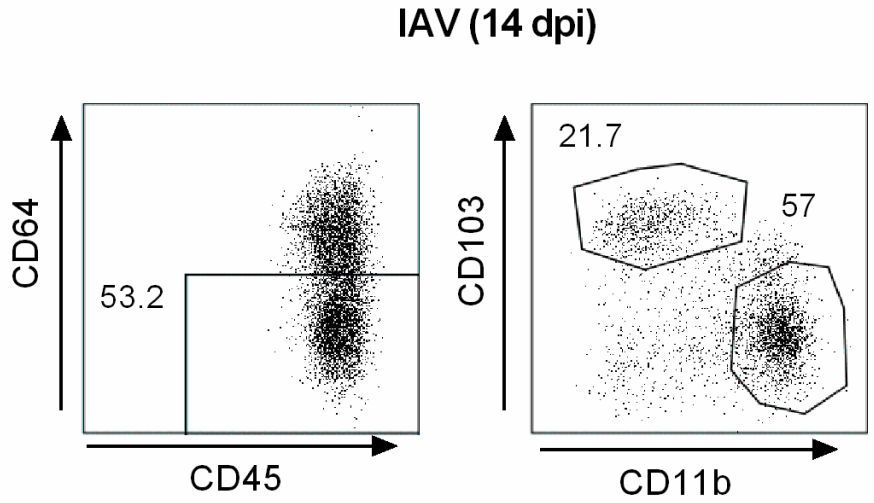


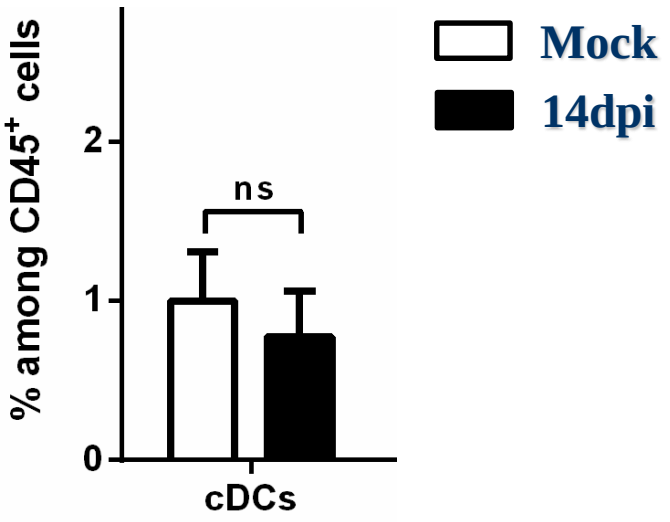
Lack of iNKT cell activation

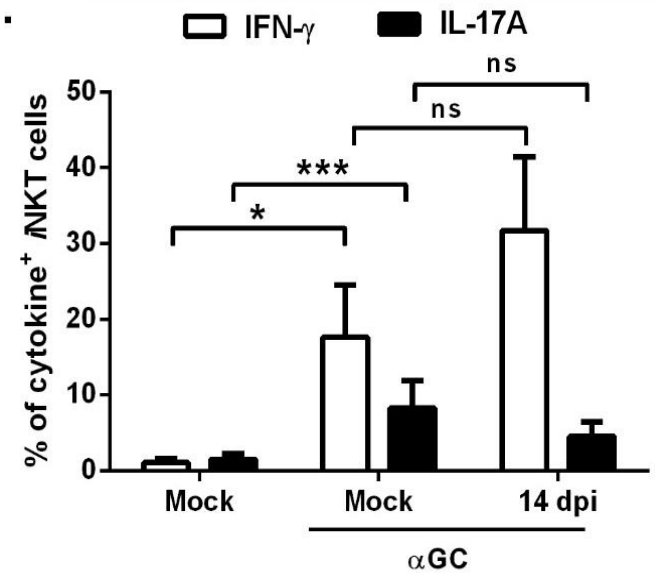
Disappearance of pulmonary CD103+ DCs at 7 dpi

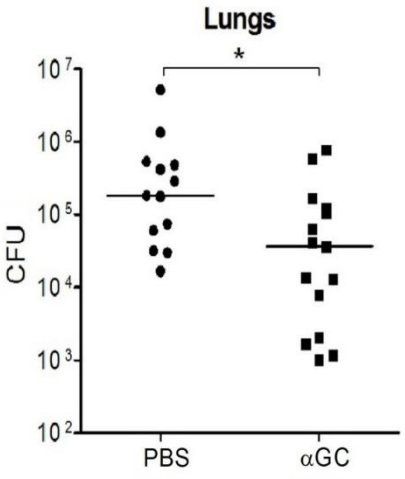


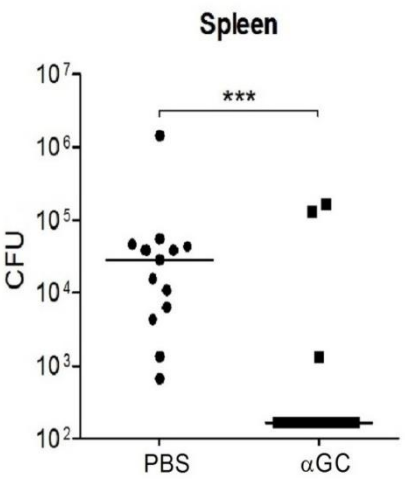
α-GalCer protects against bacterial superinfection at the resolution phase (14 dpi and therafter)



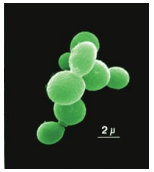








Barthelemy et al. MBio (2017)



Exogenous activation of Natural Killer T cells protects against secondary bacterial infection

Therapeutic window

→ Early phase and resolution phase

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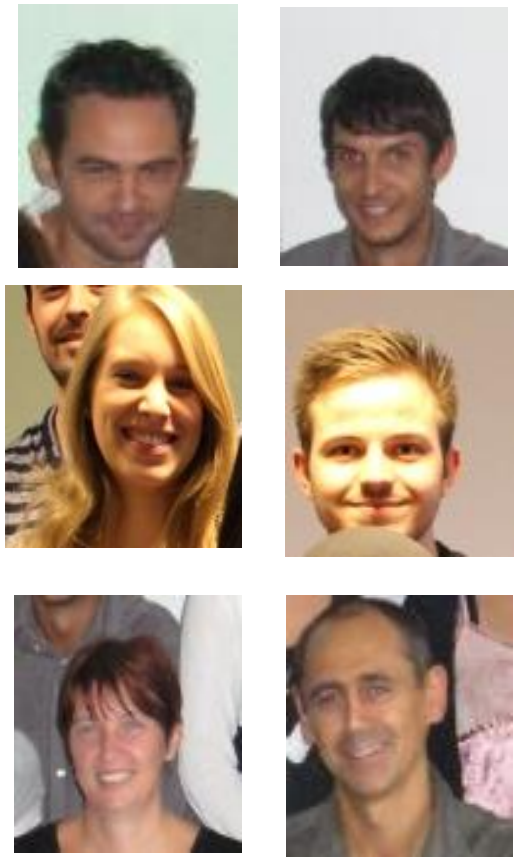

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